BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

DECEMBER 1945

THE VALUE OF PROTEIN AND ITS CHEMICAL COMPONENTS (AMINO ACIDS) IN SURGICAL REPAIR*

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THE role of protein nutrition in repair may be discussed under three headings: 1) wound healing; 2) maintenance of tissue integrity; and 3) convalescence. I shall discuss the first two topics briefly, take up the subjects of the loss of nitrogen in disease; the consequences of protein loss to the body; and the inadequacy of natural food to replenish this loss. Then I shall discuss our studies on convalescence, presenting our work in five categories. Finally, I shall discuss the role of hydrolysates and amino acid mixtures in clinical nutrition.

Wound Healing: The older work by Clark[1] and Howes[2] on wound healing was brought closer to the clinic by the series of studies by

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* Read before the Joint Session of the Section of Medicine and Section of Surgery, New York Academy of Medicine, January 16, 1945.

The work described in this paper was initiated under a grant from Mead Johnson and Company and is being continued under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and New York University. It was the product of the work of a team consisting of Drs. Arthur Mullin Wright, J. H. Mulholland (now Lt. Col., M.C., A.U.S.), Irving Barcham, George R. Gerst, and many members of the Surgical Staff of New York University College of Medicine and the New York University Surgical Division of Bellevue Hospital, as well as of Lilly Schmidt and her staff of chemists and Mary Coughlin and her nursing staff.

Ravdin and his associates[3, 4, 5, 6] on the relation between wound dehiscence and hypoproteinemia in dogs. These authors attributed wound disruption to two factors, edema and incapacity to form fibroblasts as a result of the lack of building material. Whipple[7] in 1940 in his presidential address before the American Surgical Society laid special emphasis on the relation between the lag period of wound healing and protein nutrition, and it is now the consensus of well-informed surgical opinion that protein deficiency plays an important role in wound dehiscence.

Tissue Integrity: The role of protein nutrition in the maintenance of tissue integrity was suggested by our observations on non-neurologic cases of bed sores.[8] In this study a close association was found between the occurrence of bed sores and the plasma protein level, all patients with bed sores having levels mostly below 5.5 grams per cent and never over 6.35, and a negative nitrogen balance. When the nitrogen balance was reversed from negative to positive, the bed sores healed promptly. This finding led to the formulation of the hypothesis that bed sores are pressure sores occurring in tissues which, as a result of being devitalized by protein deficiency, undergo pressure necrosis more readily than normal tissues. It must be mentioned that bed sores do not occur in cases of nephrosis, even with a plasma protein level of 3.5 grams per cent. It is possible that tissue edema, by more equally distributing the pressure, prevents this.

Production of Protein Deficiency: How is protein deficiency produced? In experimental animals it can be produced by a protein-poor diet, by plasmaphoresis, or by a combination of both.[9, 10] Clinically, similar mechanisms are operative and in addition, a third one, namely, increased metabolic loss of nitrogen as a result of injury or disease. The combination of decreased intake and increased output can deplete the protein stores in a few days.

Decreased intake may be caused by poor appetite, and it may here be said that appetite, while a good guide to nutrition in health, is a poor guide in disease. The occurrence of actual nausea, vomiting and pain also decreases intake. Then there may be poor absorption from the gastrointestinal tract as a result of diarrhea, of hyperperistalsis or of a diseased mucosa. Poor intake may also be due to neglect on the part of the attendants; that is, a physician may not prescribe an adequate diet or fail to watch the patient's nutritive status. Many surgeons have de-

TABLE I

NITROGEN CONTENT OF HOSPITAL WARD DIET

	Total nitrogen, gram
Wednesday	6.245
Thursday	14.827
Friday	8.189
Saturday	5.211
Sunday	8.6846
Monday	10.338
Tuesday	12.484
Total Nitrogen for week	65.94
Average Nitrogen per day	9.42

veloped an over-dependence on blood transfusions, expecting an occasional blood transfusion to supply a patient's caloric and nitrogen requirements for a week. Lastly, the hospital diet may be sub-standard. Charity hospitals are the greatest offenders in this respect. Table I shows the nitrogen contents of the basic diet of a charity hospital for a period of a week. This basic diet was based on Sherman's recommendation[11] for healthy individuals but has been adopted indiscriminately generally by hospitals as an adequate basic diet also for hospital patients. It will be seen that on most days the intake falls below the prescribed minimum and that the average is in the neighborhood of 9.5 grams of nitrogen per day.

Increased Metabolic Loss: The average nitrogen loss in the urine of a healthy adult is about 13.5 grams nitrogen per day.[12] This amount goes down in starvation. During disease it may go up to two or sometimes three times this figure, as found by Cuthbertson[13] and confirmed by a number of other workers, prominently among them Browne,[14] Albright[15] and Howard.[16] This increased loss has been attributed to a number of factors, among them injury and autolysis of tissues and to an endocrine factor supposed to be elaborated by the cortex of the adrenal gland. This increased loss has sometimes been called "toxic loss of nitrogen" or "catabolic loss." Whether the nitrogen lost is all replaceable has been a moot point; some workers think this can be accomplished, while others do not. As a result of recent work, it seems that the con-

TABLE II

CASES OF BURNS RE-ARRANGED ACCORDING TO PERCENTAGE OF BODY SURFACE INVOLVED

Name	*Body Surface Burned %*	*Age of Burns Days*	*Nitrogen Loss Grams Perdiem*
F.W.(1)	8	40	4.07
F.W.(2)	10	8	1.58
J.Mc.	15	21	2.98
J.W.	15	23	7.65
J.S.	15	4	1.79
A.B.	20	2	1.5
J.Mc(1)	21	15	3.56
J.Mc(2)	30	6	5.15
M.W.	40	94	6.45+
A.F.	50	4	9.07+

ditions in which this loss has been thought irreplaceable have been narrowed down. The question still remains: In what disease states and under what conditions is this metabolic loss replaceable?

Loss in Exudates: Another avenue of loss of nitrogen is in exudates and other body discharges.[17] This is comparable to plasmaphoresis in experimental animals. Table II shows the amount of nitrogen lost per twenty-four hours in cases of burns. It will be seen that A.F., with 50 per cent surface involved in burns, lost at least 9 grams of nitrogen per day (some leakage having occurred into the beddings). This represents about 55 grams of protein or about one-third of the amount present in the blood. Were it all to come acutely from the blood, this amount of loss alone would have led almost to the development of shock.

Table III shows the amount of nitrogen lost in the exudates of different surgical conditions. S. S. had an avulsion of the perineum and back, covering about 15 per cent of body surface. Three months after his injury he was still exuding 6.37 grams of nitrogen in twenty-four hours, which is equivalent to 664 cc. of plasma. R. W. was a case of radical mastectomy who lost 4.26 grams of nitrogen in the first twenty-four hours, dwindling down to 1.2 grams in three days. A. G., who had an abdomino-perineal resection for carcinoma of the rectum, lost 6.22 grams of nitrogen in the first twenty-four hours. This loss had decreased

TABLE III

NITROGEN LOSS IN DIFFERENT EXUDATIVE SURGICAL CONDITIONS

Name	*Diagnosis*	*Date of Injury or Operation*	*Date Collect.*	*Total N Exuded 24 hrs., gm.*	*Equiv. in Proteins gm.*	*Equiv. in Plasma cc.*
S.S.	Avulsion Perineum and Back	7/7	10/23	6.37	39.81	664
R.W.	Radical Mastectomy	10/25	10/26 10/30	4.26 1.2	26.65 7.50	445 125
A.G.	Abd-Perineal Resection (Cancer-rect)	8/13	8/14 8/16	6.22 2.07	38.87 12.97	644 216
O.Mc.	Abd-Perineal Resection (Infected Cancer-rect)	8/9	8/18 8/21	6.97 3.47	42.46 21.69	707 723
F.C.	Lung Abscess Pyothorax		4/24	9.57—	59.8—	996
A.C.	Empyema			9.37	58.56	976
H.L.	Liver Abscess (5 cm. diam.)	12/26	12/28	1.98	12.63	210

to 2.07 in twenty-four hours. Both of these cases suggest an effort on the part of the body to seal off exuding surfaces. O. Mc. was a case of abdomino-perineal resection which was infected. The loss in the pus nine days after operation was 6.9 grams but within three days after drainage was instituted, it had decreased to 3.47 grams. F. C. and A. C. were, respectively, cases of lung abscess with pyothorax and of empyema. They lost respectively 9.57+ and 9.37+ grams, equivalent to almost 1,000 cc. of plasma or about one-third of the amount of circulating protein in the blood. This magnitude of loss may in part account for the emaciation and high mortality observed in this type of case. Our experience with the burn cases makes us hopeful that chest cases of this type may respond favorably to full nitrogen replacement.

Consequence of Large Protein Loss: Some of the consequences of large protein loss have been implied in the remarks on wound healing and on the maintenance of tissue integrity and need not be repeated. When the loss is large and acute, such as that which occurs in burns, the osmotic component of the blood can be so depleted as to cause shock.

TABLE IV

NITROGEN VALUES OF VARIOUS HOSPITAL DIETS

	Protein gm.	*Total N gm.*	*N in gm. kgm.*
Basic	70	11.2	.186
High Protein (1)	120	19.2	.32
High Protein (2)	130	20.8	.346
Tolerance[1]	192	30.7	.512

[1] By tolerance is meant the amount taken to the point of satiety.

In the cases of more chronic losses, although the hypovolemia may be better tolerated, the patient must be expected to be a poorer risk as a result of the hypovolemia.

The blood plasma level does not always indicate a diminished total blood protein but it may be safely stated that a blood plasma protein below 6.0 grams per cent is indicative of protein deficiency. Five grams per cent is usually called the critical level of clinical edema.[10]

Digestive disturbances in the form of delayed emptying time and even of vomiting and diarrhea[6] may be symptoms. This would cause a vicious circle in further decreasing the intake.

There is also evidence to show that antibody formation is hindered.[18]

A set of mental symptoms in the form of confusion, apathy and incontinence of urine and feces has also been noted to be associated with protein deficiency.

Lastly, convalescence appears to be retarded by protein losses which are not replaced, resulting in long continued weakness and incapacitation. This we shall discuss later.

Inadequacy of Natural Food: Assuming that the replenishment of the nitrogen lost is both desirable and feasible, the question arises as to the adequacy of natural food for this purpose. Table IV shows the range of nitrogen values of the standard hospital diets. It will be seen that the ceiling of nitrogen intake is set by the "high protein diet" which contains approximately 20.8 grams of nitrogen. Considering that it takes more than 1 gram of nitrogen in the intake to replace 1 gram of nitrogen lost from the body, it is readily understandable how inadequate this

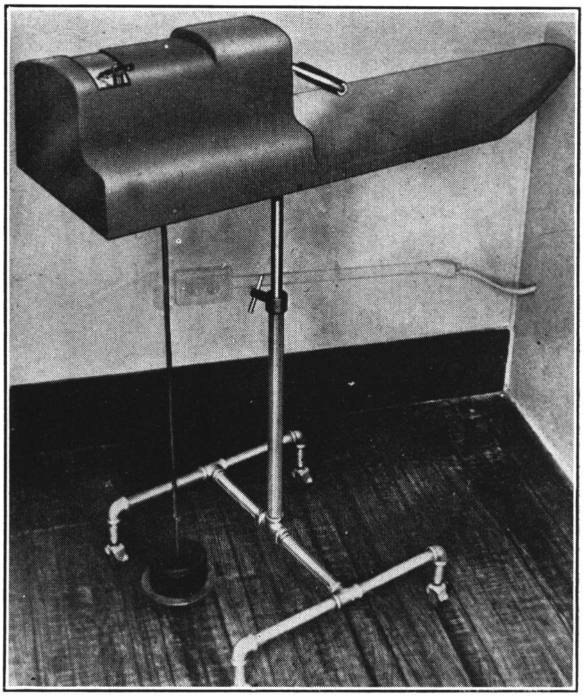

Fig. 1. Improved bedside ergograph with mechanism enclosed.

"high protein diet" is to a person who is losing 20 grams of nitrogen in the urine and 6 to 9 grams in an exudate. The gap between the low ceiling of nitrogen intake possible with natural food and the large losses occurring in trauma and disease can be filled to a fair degree of adequacy by protein hydrolysates such as amigen.

Convalescence: I shall now take up our studies on convalescence in five clinical categories; namely, burns, gastrectomy, herniotomy, cholecystectomy, and finally peptic ulcer; and incidentally show the value of hydrolysates. Except for the cases of burns, the complete nitrogen balance was followed in all of the cases for from a week to twelve days. Also determined were the body weight and in many cases, the endurance as tested by the bedside ergograph.

The original model of this ergograph was described in a previous communication.[19] The improved model is shown in Figure 1. The E.T. or ergograph time is the number of seconds a patient is able to lift a known weight until fatigue sets in. Objection to the use of the ergograph has been advanced on the basis that both motivation and the

TABLE V

NITROGEN INTAKE IN PATIENTS WITH BURNS FED WITH PROTEIN HYDROLYSATES

Patient	*Original Body Wgt. Kgm.*	*Area Burned %*	*Total Daily N Intake gm.*	*N in gm. Wt. Kgm.*	*Equiv. Plasma cc.*	*Remarks*
J.C.	56.8	10	35	0.62	3644	Sufficient
J.McN.	55.45	30	24	0.43	2500	Insufficient
			25.6	0.46	2650	Insufficient
			33.6	0.61	3500	Maintenance
			42.2	0.76	4400	Rapid Gain
M.W.	65.9	50	27.44	0.42	4570	Insufficient
			36	0.55	3750	Maintenance
			49.5	0.75	5160	Slight Gain
			66	1.00	6875	Rapid Gain

learning process, which have been found to affect ergography on normal subjects, may introduce sources of error in tests in convalescence. However, the factor of motivation in severely ill patients may be considered a minor one, since most patients are eager to show as good results as possible. The matter of training may also play but a small part, since these tests were made not more often than once in two or three days. In any event, the results have been striking and consistent, showing a gradual increase when the patient improved and was on positive nitrogen balance, and a decline when the patient declined and was on negative nitrogen balance.

The period of recumbency has also been taken as a criterion of recovery, although it is only a relative one, since the practice of forced early ambulation has itself shortened convalescence, perhaps by stimulating appetite and promoting an earlier establishment of positive nitrogen balance. The patients reported in these five groups were all from a surgical service that does not practice early ambulation, so that the factor of more prolonged bedrest is common to all.

Burns: I shall first take up three cases of burns as shown in Table V which have been reported elsewhere.[20] It will be seen from the table that there seems to be a fairly close relationship between the area of burned surface and the amount of nitrogen intake necessary to maintain nutrition. Thus, J. C., who had only 10 per cent of his body area burned,

TABLE VI

LOW NITROGEN INTAKE POSTGASTRECTOMY

Name	*N Intake Wt. gm.*	*N Loss Wt. x Day gm.*	*Days Under Study*	*Loss of Wt., Kg.*	*Return of E.T., Days*	*Days in Bed*	*Remarks*
P.B.	.04	.153	8	4.27		23	
F.Mc.	.04	.015	12	6.59	Not 12th	17	
J.S.	.04	.207	8	3.89		17	
D.F.	.052	.165	11	.9		35	Evisceration
N.G.	.06	—	12	7.8		24	
A.D.	.07	.183	10	4.78		19	
G.W.	.08	.089	13	5.26		17	
R.B.	.095	.159	8	.48		21	
F.W.	.095	.065	12	4.45		21	
M.K.	.11	.237	9	6.19	Not 12th	13	Amigen-prepared
W.C.	.18	.088	9	4.05		13	Amigen-prepared
J.B.	.19	.078	10	1.7		37	
A.S.	.27	.015	9	4.37		17	
			Average Days	....		21.07	

was able to support nutrition on 35 grams of nitrogen in the form of amigen. For J. McN. with 30 per cent of body surface burned, 25.6 grams nitrogen was insufficient, 33.6 maintained nutrition, whereas 42.2 resulted in rapid gain. M. W. with 50 per cent of body surface burned, lost ground on 27.44 grams nitrogen, was maintained on 36 grams, registered slight gain at 49.5, and rapid gain at 66. All these values are much larger than the amount of nitrogen available in even the hospital high protein diet.

Gastrectomy, Cholecystectomy and Herniotomy: The next series were gastrectomy cases. There are thirteen cases on low protein intake in Table VI, the intake ranging from .05 to .27 grams of nitrogen per kilogram body weight. The nitrogen losses/KBW ranged from .015 grams [.19 GM/KBW] in the case of F. Mc. to .237 in the case of M. K. The body weight loss ranged from .48 kilograms in the case of R. B. to 6.59 kilograms in the case of F. Mc. The strength as measured by the

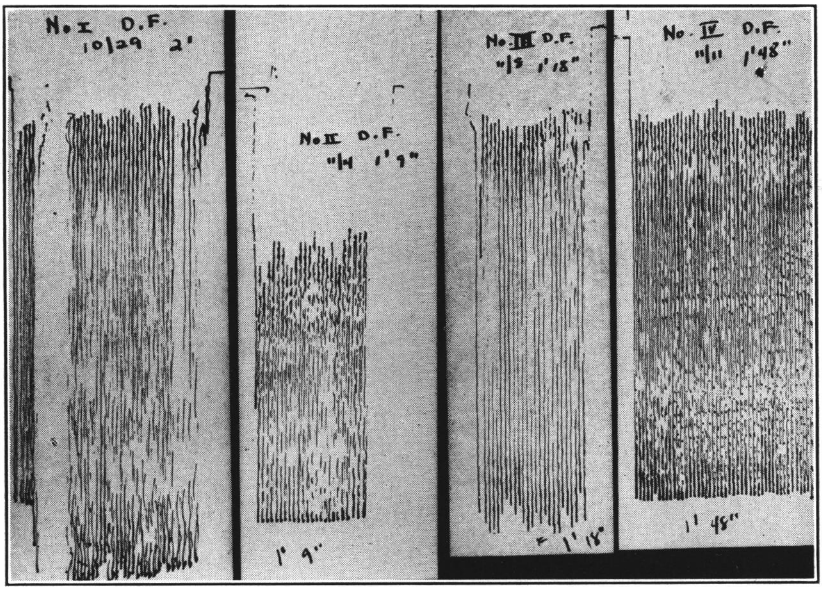

Fig. 2. Ergogram of Patient D.F. (Table VI). Low protein intake postgastrectomy. Initial ergogram: E.T. was 2′. The three subsequent ergograms were respectively 6, 10 and 13 days after operation. Note that on the thirteenth day, E.T. had not returned to the initial reading.

TABLE VII

HIGH NITROGEN INTAKE POSTGASTRECTOMY

Name	*N Intake Wt. gm.*	*N Gain Wt. x Day gm.*	*Days Under Study*	*Wt., Gain kgm.*	*Return of Endurance*	*Days in Bed*
A.V.	.25	.069	7	1.14		22
G.H.	.42	.049	13	2.2		13
V.B.	.434	.169	12	4.71		14
P.R.	.44	.077	8	4 54		8
G.S.	.44	—	8	6.0		8
A.V.	.48	.14	11	4.54	Before 8th	9
F.R.	.482	.217	11	3.95		17
A.H.	.5	—	—	4.0		10
C.N.	.6	.212	12	5.3	Before 8th	10
R.B.	.6	.241	10	4.32	Before 8th	10
E.B.	.61	.303	11	5.85		10
P.F.	.692	.2	12	4.21		14

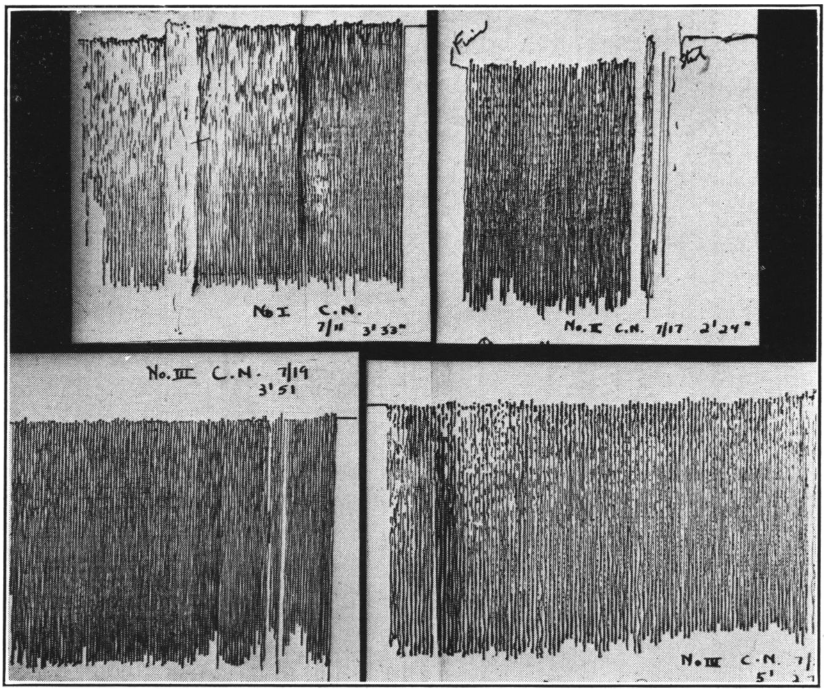

Fig. 3. Ergogram of Patients C.N. (Table VII). High protein intake, gastrectomy case. Panel I is the initial ergogram. Subsequent ergograms, 4, 6 and 12 days after operation. Note that by the sixth day, the E.T. had topped the initial reading.

ergograph had not returned by the twelfth day in any of the patients tested. Figure 2 shows one such an ergogram. The average number of days which the patient stayed in bed was 21.07. M. K. and W. C. were both fed with amigen until they felt strong and gained weight at least a week before they were sent to the operating room. Their ability to get up in thirteen days indicates the importance of the pre-operative period of up-building and the usefulness of hydrolysates in the up-building of malnourished patients.

Table VII summarizes twelve similar cases on high nitrogen intake following gastrectomy, the nitrogen and caloric intake again consisting of amigen and dextri-maltose fed for the first four to six days through the jejunal lumen of a double-lumened tube, the other lumen lying in the stomach for the purpose of keeping the viscus deflated. After withdrawal of the tube, the feeding was given orally. It will be seen that the level of intake was .25 grams of nitrogen/KBW or over. All the patients were in positive nitrogen balance, gaining from .069 grams of nitrogen per KBW in the case of A.V. to .3 in the case of E.B. The weight gain ranged from 1.14 to 6 kilograms. The endurance returned by the eighth day, and Figure 3 shows the ergogram of C.N. The number of bed days averaged 12.8, an average which was not quite fair since any attempt at a reduction of bed days in patients of this type runs counter to surgical tradition and is usually resisted, eventually resulting in a prolongation of bed rest. The final number of eight to nine days is therefore the more faithful time of bed rest.

Putting these two tables together, one finds that under an intake of .19 GM KBW the patients were always in negative nitrogen balance and lost weight and that the E.T. declined significantly in all the cases tested. One patient, A.V., with an intake of .25 grams nitrogen per KBW* was in positive balance, whereas another patient, A.S., was in negative balance on .27 grams nitrogen per KBW, denoting that there is an intermediate zone in which some cases will register a negative balance while others, a positive balance. All patients having an intake of .42 grams per KBW and over were in positive nitrogen balance and all gained weight; and all those tested showed an early return of endurance as shown by the early decrease of E.T. Both of these tables were rearranged from tables which appeared in two previous reports.[20, 21]

The third series of cases were cholecystectomy cases which are represented in Table VIII under both low and high intakes. In this series, when the intake was below .224 grams per KBW, there was a negative balance, whereas above .339 grams per KBW, there was always positive nitrogen balance. The weight and ergogram show the same trend as in the gastrectomy cases. This series is still too small, as there is too large a gap between the unit intakes of .224 and .339 grams per KBW.

The last series are seventeen cases of hernioplasty, twelve unilateral and five bilateral. This study was undertaken not because the nitrogen loss after herniotomy is an apparently important factor in convalescence but to test the theory that normal persons subjected to operative trauma undergo a nitrogen loss which cannot be replaced. Most of these patients were in good nutrition, so that except for their structural defects, they may be considered normal persons who had suffered operative trauma.

Table IX summarizes the nitrogen balance studies. Part A embodies the twelve cases of unilateral hernioplasty and Part B, the five of bi-

* In the balance of this paper "KBW" will denote Kilogram Body Weight.

TABLE VIII

NITROGEN INTAKE POST-CHOLECYSTECTOMY

Name	*N Intake Wt., gm.*	*N Gain or Loss Wt. x Day*	*Days Under Study*	*Wt., Gain or Loss (kgm.)*	*Return E.T. (day)*	*Bed Days*
A.C.	.089	—.104	12	—3.9		35
A.J.	.058	—.12	10	—2.8	not on 14th	18
M.R.	.224	—.026	14	—1.36		19
R.V.	.339	.168	10	2.74		10
P.F.	.348	.143	10	2.77		12
E.S.	.382	.082	12	1.2		12
L.M.	.402	.3285	10	3.7	6th	8
A.S.	.43	.049	10	1.17	8th	10
F.S.	.456	.204	12	1.0		12

TABLE IX

UNILATERAL HERNIOPLASTY: Group A

Name	*N Intake gm. per kgm.*	*N Balance per day*	*Number of Days*	*Wt. Change (kgm.)*	*E.T.*
A.S. (1)	.059	—.111	9	—1.02	
(2)	.087	—.086	9	—1.59	
A.B.	.104	—.06	10	—1.37	273-243
O.V.	.131	—.07	10	—1.5	377-260
V.P.	.147	—.011	10	— .45	
J.B.	.182	.011	10	— .37	500-510
H.G.	.258	.002	10	.5	372-390
P.N.	.35	.046	10	0	
W.J.	.363	.045	7	?	
M.S.	.38	.11	10	2.01	
J.F.	.45	.131	10	2.02	
D.F. (1)	.446	.127	10	2.22	
(2)	.454	.147	8		
J.D.	.53	.033	10	1.59	
BILATERAL HERNIOPLASTY: Group B					
A.T.	.13	—.152	10	—2.9	
S.J.	.156	— .072	10	—2.27	
B.A.	.335	.066	8	.9	
C.L.	.373	.003	10	.3	
J.F.	.395	.004	10	.31	

lateral. A.S. and D.F. in Part A both had bilateral hernias, one of which was operated upon several days after the other. It will be seen that at the second operation the loss of nitrogen in grams per KBW did not differ radically from the first operation a week or so earlier. It will also be seen that on an intake of .182 grams per KBW, there was a negative nitrogen balance. The ergograph time (E.T.) in this group with the negative nitrogen balance was significantly depressed in one, O.V., and very slightly but not significantly in two; that above .258 grams per KBW there was a consistent positive nitrogen balance with gain in weight.

A comparison of the nitrogen loss or gain per KBW in simultaneous, bilateral hernioplasty with that in unilateral hernioplasty is interesting. Thus, if we match A.T. in Group B, intake .13 grams per KBW, with O.V. in Group A, intake .131 grams per KBW, we see that A.T. lost .152 grams nitrogen per KBW, as compared with the loss of only .07 grams in O.V., and the weight loss of the former was 2.9 kilograms as compared with 1.5 in the latter. S.J. in Group B, with an intake of .156 grams per KBW, if matched with V.P. in Group A, who had an intake of .147 grams per KBW, lost .072 grams nitrogen per KBW, while V.P. lost only .011 grams. The weight loss of S.J. was 2.27 Kgm. as compared with the loss of only .45 Kgm. in V.P. Again, if C.L., with unit intake of .373 grams of nitrogen is matched with W.J. with unit intake of .363 it is seen that C.L. gained only .003 grams of nitrogen per KBW, whereas W.J. gained .045. Lastly, if J.F., Group B, with intake of .395 grams per KBW is matched with M.S. on .38 grams per KBW, it will be seen that the former gained only .004 grams per KBW, whereas the latter gained .11 grams.

These figures suggest that the loss of nitrogen in hernioplasty may not all be attributable to the nitrogen loss due to bedrest and that the extent of operative trauma plays a role. It also shows that the post-operative loss of nitrogen, even in previously normal persons, is correctable, at least in some types of cases. Both Elman[22] and Peters[23] have also found that cases of hernioplasty can be readily put into positive nitrogen equilibrium.

Parenthetically, the hope may be expressed that herniotomy cases in good nutrition, because of the fairly well standardized surgical trauma inflicted, may be used to compare the biological value of different hydrolysates on the human body. Thus, if a hydrolysate X cannot support

N equilibrium at a level of intake of about .182 grams nitrogen per kilogram body weight, it would be inferior to amigen, while one which can do this at a lower level might be considered of superior biological value.

A correlated view of the studies of these four surgical categories; namely, burns, gastrectomy, cholecystectomy and herniotomy, suggests that there may well be a critical level of nitrogen intake peculiar to each category to maintain the patients in nitrogen equilibrium. Only a further study will confirm or refute this possibility.

Peptic Ulcers: The fifth series of cases is of peptic ulcers treated with protein hydrolysates and high caloric diet. The series of twenty-nine cases may be classified as follows:

16	duodenal ulcer
5	duodenal and gastric ulcer
6	gastric ulcer
2	gastro-jejunal ulcer
29	
13	"intractable"
6	with retention (20-100%)
6	with frank hemorrhage

All were treated with from .5 to .6 grams nitrogen per KBW, in the form of amigen, and enough dextri-maltose to make up to 40 C per KBW. This is approximately 5 grams each of amigen and dextri-maltose per KBW. The mixture is suspended in water, divided into eight to nine feedings, and given at two-hourly intervals. Feedings were continued two or three weeks exclusively, depending upon the clinical response and x-ray findings. No antacids or antispasmodics were given, and wherever necessary, amphojel in 4 cc. doses was given twice a day to control diarrhea. A full complement was added to the feeding. The results may be summarized as follows:

Pain and distress stopped in twenty-four to forty-eight hours. Vomiting stopped forty-eight hours after institution of the feedings; rapid roentgenologic healing; positive nitrogen balance, averaging 10 to 16 grams (first ten days); gain in weight, 1 to 8 Kilos in two to three weeks; and rapid gain in strength and morale. However, the treatment does not prevent recurrence on resumption of old dietary habits.

Figures 4 and 5 show the progression of healing in two gastric ulcer cases. One interesting feature in connection with these ulcer cases is the great improvement in endurance as may be seen in the ergogram of patient E.B. in Figure 6.

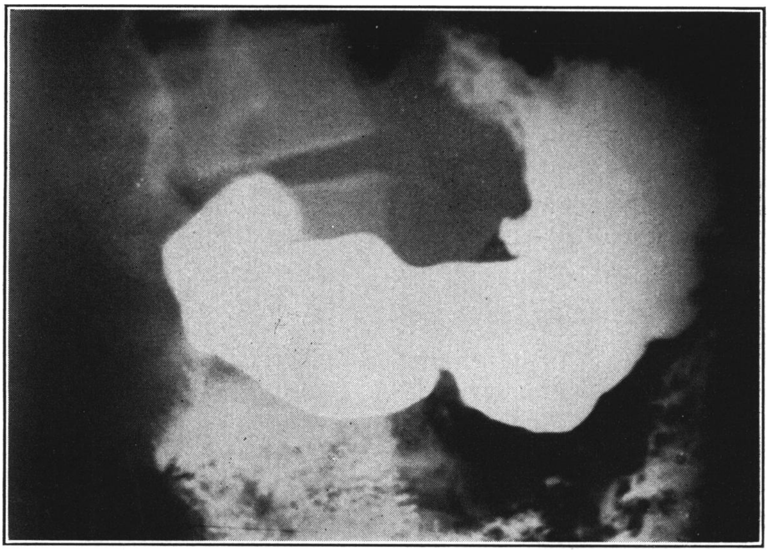

Figure 4A. Patient C.B. Large crater, lesser curvature.

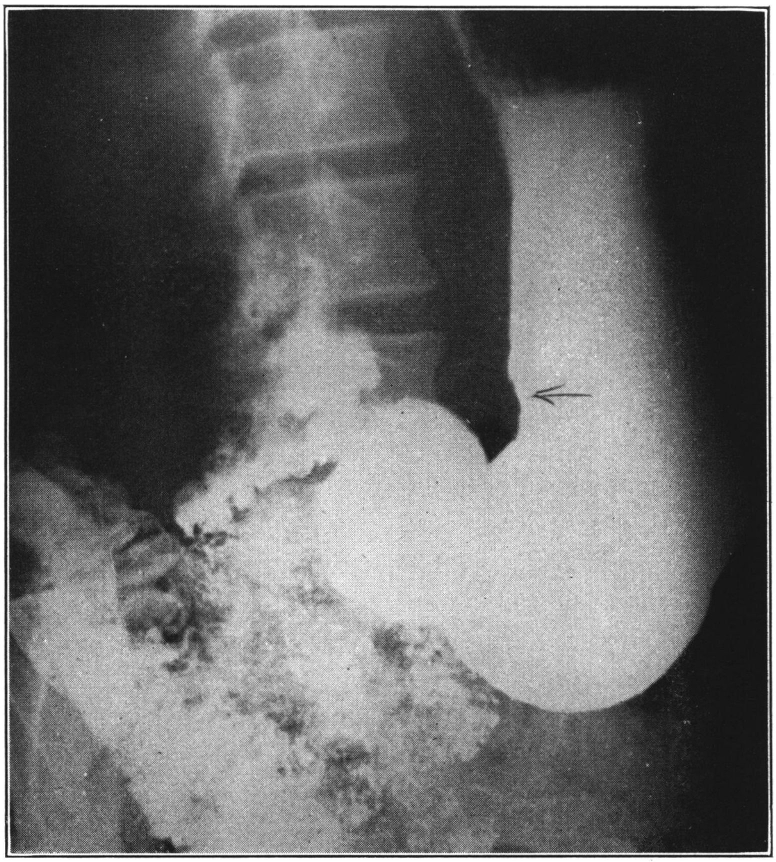

Fig. 4B. Patient C.B. Almost complete healing in 10 days.

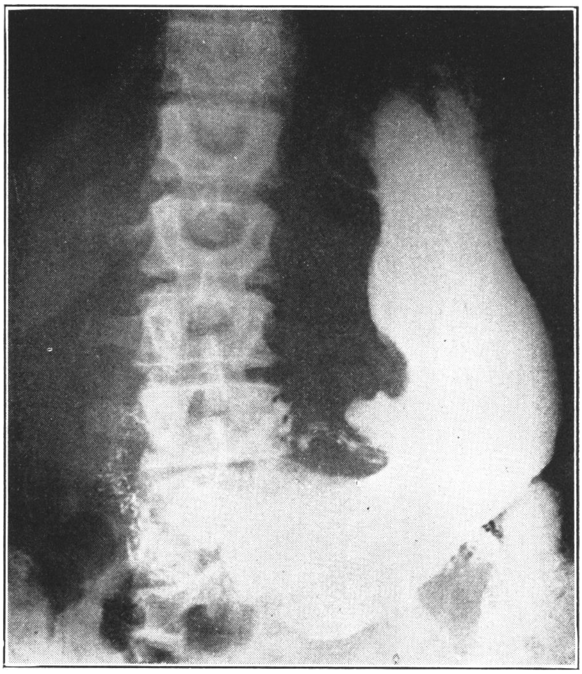

Fig. 5A. Patient R.B. Large ulcer crater, lesser curvature pars media.

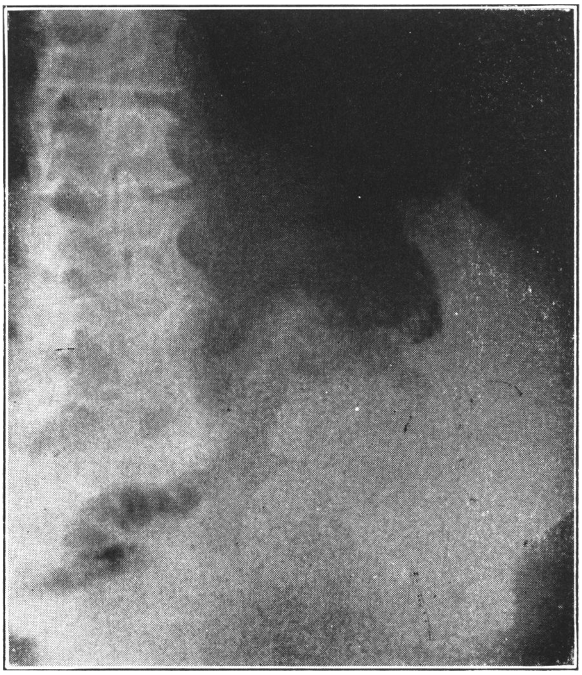

Fig. 5B. Patient R.B. Shows gradual filling up of defect 10 days after treatment.

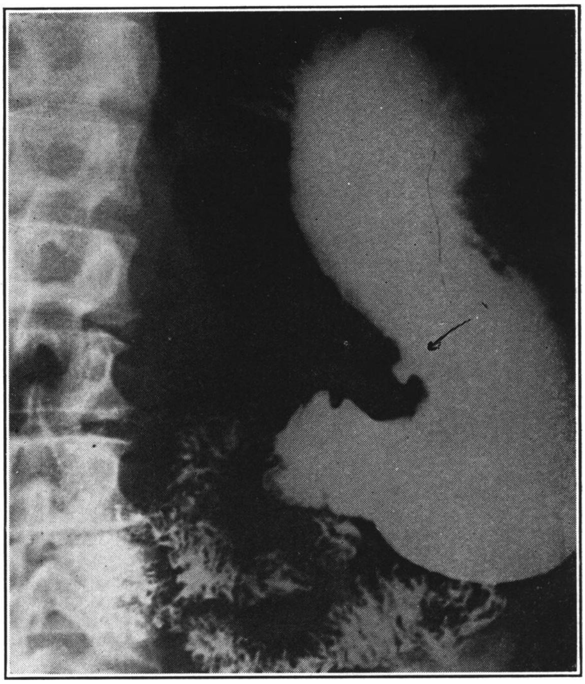

Fig. 5C. Patient R.B. Four weeks after treatment. Note nipple-like defect.

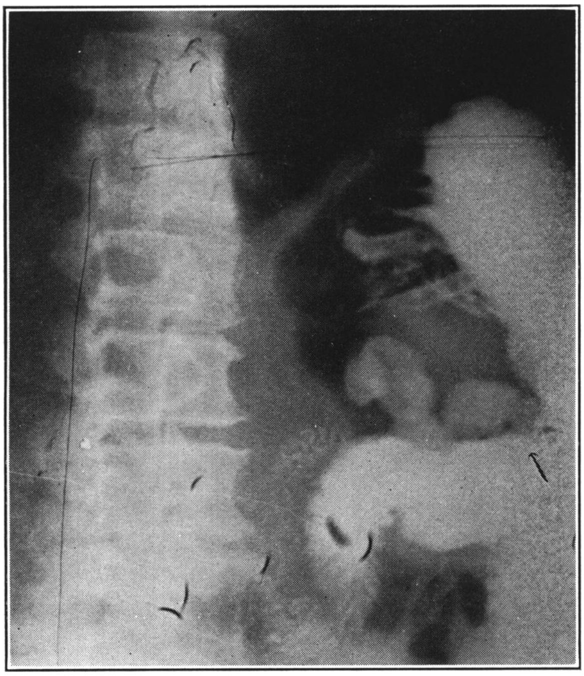

Fig. 5D. Patient R.B. Six weeks after treatment. Note stalk-like defect.

Fig. 5E. Patient R.B. Seven and a half weeks after treatment. Note almost complete healing.

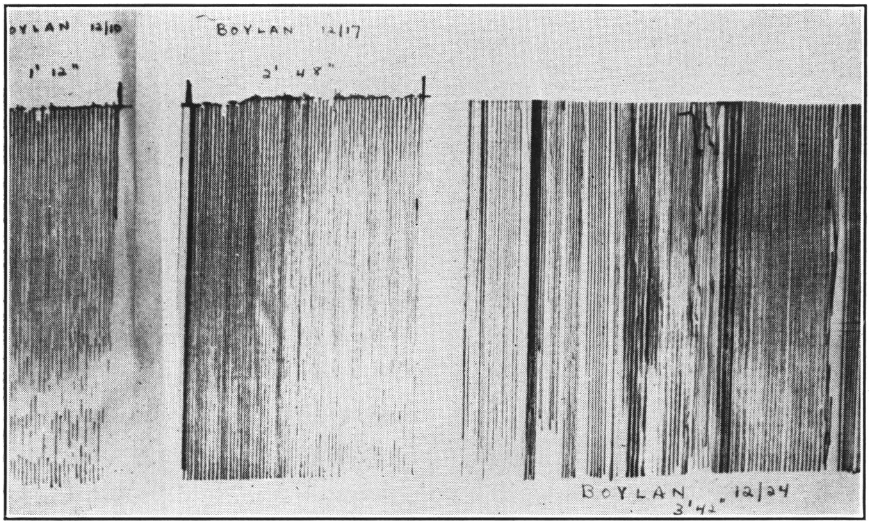

Fig. 6. Ergogram of ulcer patient C.B. Panel (a) initial ergogram, E.T. 1′2″; Panel (b) E.T. 2′48″, 6 days after treatment; Panel (c) E.T. 3′42″, 2 weeks after treatment.

TABLE X

EFFECT OF FEEDING MIXTURE ON pH AND FREE ACIDS IN THE GASTRIC JUICE OF A PEPTIC ULCER PATIENT

Time	*pH*	*F.A.*	*T.A.*
10:00	2.05	47.0	65.5
10:10	1.92	59.0	78.5
Feeding: 10:10			
10:45	4.21	—	205.5
11:00	4.24	—	269.5
11:15	4.15	—	245.5
11:30	4.07	—	305.0
11:45	4.22	—	298.0
12:00	4.18	—	286.5
12:15	3.68	3.0	212.5
12:30	3.01	34.5	191.5
Amigen: 51.1 g. Dextri-maltose: 58.6 g.			
Formula	5.22	—	456.0

Another feature of this treatment is that where obstructions were found in the six-hour x-ray plates, they were relieved in twenty-four hours by amigen feeding. The significance of this point will be commented on later.

The question arises: What is there in protein hydrolysate feeding which may account for these prompt results? Amigen is an amphoteric substance and the addition of it to a hyperacidic gastric juice raises the pH to almost the point of abolition of peptic activity. Table X shows that the pH of a gastric juice, originally between 1.92 and 2.05, was raised by the feeding of a mixture of 51.1 grams of amigen and 56.8 grams of dextri-maltose to 4.24. The free acid originally was reduced to zero for about an hour and fifteen minutes. After that, the pH began to decline and the free acid to rise. It is perhaps this action of neutralization of the acid in connection with the giving of a rich nutrient solution to enable the body to build up its tissue deficiency which accounts for the prompt healing in these cases. Thus it seems that by the peculiar virtue of its being both an antacid and a rich nutriment,

TABLE XI

PATIENT WITH GASTRO-JEJUNOCOLIC FISTULA FED WITH PROTEIN HYDROLYSATES

A.S. Date 1942 Feb. 29 to March 1	*N Intake*	*Nitrogen Output*			*N Bal. gms.*	*P.P. gms. % A/G*	*Wt. Kgms.*	*Remarks*
		Urine N gms.	*Fecal N gms.*	*Total N Output gms.*				
March 1	11	10.28	3.36	13.64	—2.64	5.25	47.9	Lost 15 lb.
1-2	8	9.42	4.41	13.83	—5.83			3 weeks x-ray:
2-3	9.4	8.74	4.85	13.59	—4.19	5.15	47.3	G-J-C- fistula
3-4	14.58	10.61	1.04	11.65	2.93			"Stronger"
4-5	14.58	11.38	1.03	12.69	1.89		47.8	
5-6	8.46	7.24	1.58	8.82	—0.36			
6-7	8.8	7.94	1.14	9.08	—0.28		47.3	"Weaker"
7-8	18.9	16.85	1.06	17.91	.91	5.25		
8-9	18.9	13.27	1.21	14.48	4.42			
9-10	18.9	14.08	1.47	15.65	3.25			
10-11	18.9	15.18	1.37	16.55	2.35			
11-12	18.9	15.06	1.45	16.51	2.39			
12-13	18.9	14.87	1.26	16.13	2.77			
13-14	18.9	16.48	1.48	17.96	0.94	6.1	49.1	x-ray: healed "strong"

amigen and perhaps other hydrolysates are specially suitable for the treatment of peptic ulcer.

Value of Hydrolysates: The studies in the cases of burns, gastrectomy, cholecystectomy and herniotomy show how valuable hydrolysates are in conditions in which natural food cannot be ingested or ingested only in quantities insufficient to replace increased nitrogen loss due to disease. Whereas the nitrogen intake in the natural diet is generally limited to the 20.8 grams (.34⅔ grams/KBW for a 60-Kgm. man) in the high protein diet, the intake possible with protein hydrolycates may be many times that amount. By the intravenous route, 3 liters of a 5 per cent amigen may be safely given. This is equivalent to .3 grams/KBW. By mouth, it has been found that most patients can tolerate as much as .8 grams of nitrogen per Kgm. without having diarrhea.

If both routes are simultaneously utilized, a total of 1.1 grams of nitrogen per KBW may be given, over 500 per cent of the intake possible with natural food. It is quite possible that further research in this field will make available a product which can be given in greater concentration and which will be of maximum human biological value, thus further raising the ceiling of replenishment.

However, hydrolysates have another field of usefulness. The cases of pyloric obstruction following peptic ulcer which were relieved twenty-four hours after amigen feeding, suggest that hydrolysates are better tolerated by a diseased gastro-intestinal tract than natural food. Additional evidence for this may be seen in Table XI which summarizes the nitrogen balance study of A.S., a 48-year old man who was admitted with a gastro-jejuno-colic fistula, having lost 15 pounds in three weeks. During the first three days on the natural diet, the patient was losing in the stool from 3.36 to 4.85 grams of nitrogen per day or almost half of his intake. This was accompanied by negative nitrogen balance, weakness and loss of weight. He was then put on amigen by mouth, taking an amount corresponding to 14.58 grams of nitrogen daily. This was followed by a reduction of fecal loss of nitrogen to over 1 gram and a sense of returning strength and well-being. The intake was again reduced to 8.46 for two days, at which time he was again in negative balance and feeling weaker. After that, on an intake of 18.9 grams of nitrogen, he was on positive nitrogen balance which continued for about a week, at which time the x-rays showed the fistula to be apparently healed.

We may also mention three cases of ulcerative colitis treated with amigen, in whom the nutrition was maintained although the pathological condition was not improved.

A case of pernicious vomiting of pregnancy may also be reported. A tube was passed into the stomach through one nostril and amigen feeding was instituted, at which time the vomiting stopped. This feeding was continued for three days until the nasal irritation caused by the tube became so marked that the tube had to be withdrawn. The tube was replaced in another twenty-four hours through the other nostril and a feeding period of three days was instituted. Thus a "lean" period of one day alternated with a "fat" period of three days until after four weeks the patient was able to tolerate food. The patient went to term uneventfully. This better tolerance on the part of a pathologic gastro-intestinal tract for hydrolysates may be expected, since it is spared the task of having to take food apart and since the minimum of digestive effort is called for before absorption takes place.

One is led to speculate how worthwhile it would be to try feeding this substance in other conditions in which the gastro-intestinal tract cannot tolerate natural food, such as sprue, typhoid fever, etc.

In the use of hydrolysates one has to make sure that in the intravenous form they are not toxic, not anaphylactogenic, non-pyrogenic, and non-irritating to the site of injection. In the oral form, efforts are still being made by manufacturers to produce a good-tasting preparation and one which can be given in large amounts without causing diarrhea or vomiting. For both oral and intravenous preparations we must insist that they maintain positive nitrogen balance in the human being. Finally, the clinician who uses them must think quantitatively not only in terms of nitrogen but in terms of adequate caloric intake. Otherwise, the results will not be satisfactory.

Assay of Protein Nutritional Status: In conclusion, some general comments on the assay of the nutritional course of a convalescent patient may be pertinent. At present there are four likely methods of doing this: 1) nitrogen balance; 2) plasma protein curve; 3) body weight curve; and 4) the bedside ergograph.

Nitrogen balance determinations require a tedious and rather complicated chemical procedure not available to the average hospital. It depends for its validity on a bookkeeping process which as evidence is at best only circumstantial and not directly concerned with the effects on the body occasioned by the nutritional state.

The other three methods are more closely connected with assay of the body status. However, none of these methods is sensitive. A large amount of plasma protein could be lost from the blood without its being reflected in the plasma protein level, and hydration and dehydration can cause marked swings in the values. The body weight is also subject to the factors of hydration, to retention of urine and feces. It is inconvenient and not easily measured in the bed patient without adequate personnel.

As mentioned before, the ergograph has the theoretical objections of motivation and the learning factor. However, it has seemed to us that the changes in endurance produced by nitrogen loss are so striking that the ergograph findings transcend these two factors. The ergograph determinations are sensitive enough to be of clinical usefulness, and in conjunction with the other three methods, the ergograph is a valuable tool. Serial readings of all three are more valuable than single determinations.

Summary

1. Proteins are essential to wound healing, to the maintenance of tissue integrity; and from present indications, to expeditious convalescence. Protein deficiency endangers all three.

2. A patient can become protein-deficient as a result of inadequate intake and increased nitrogen output or a combination of these two factors.

3. Decreased intake may be due to the patient or neglect on the part of the attending staff.

4. Increased output may be due to increased metabolic loss and to the loss through exudates.

5. The ceiling of nitrogen intake in natural food is naturally low and consequently natural food is often inadequate to replenish the increased protein loss in disease and injury.

6. Studies on cases of burns, of postoperative gastrectomy, cholecystectomy and herniotomy, suggest that convalescence can be shortened, strength and weight conserved by full caloric and nitrogen replacement immediately postoperatively; and that there may be a critical range of nitrogen intake for each disease category.

7. The protein hydrolysates, by raising the ceiling level of nitrogen-intake, are indispensable in many disease conditions and can be used with greater elasticity than natural food.

8. In the course of study on the value of protein hydrolysates, a new treatment for peptic ulcers has been evolved.

9. Protein hydrolysates for clinical use must fulfill a number of criteria and clinicians using them must be quantitatively-minded.

10. A discussion on the assay of the nutritional course of convalescent patients has been attempted.

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